

## Exhibit 6



A service of the National Library of Medicine  
and the National Institutes of Health

My NCBI  
[Sign In] [Regis]

All Databases: PubMed Nucleotide Protein Genome Structure OMIM PMC Journals Book

Search PubMed for

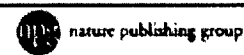
Go Clear

Limits Preview/Index History Clipboard Details

Display AbstractPlus Show 20 Sort by Send to

All: 1 Review: 0

1: Bone Marrow Transplant. 2007 Mar 12; [Epub ahead of print]



Links

### Rapamycin, not cyclosporine, permits thymic generation and peripheral preservation of CD4(+)CD25(+)FoxP3(+) T cells.

**Coenen JJ, Koenen HJ, van Rijssen E, Kasran A, Boon L, Hilbrands LB, Joosten I.**

[1] 1Department of Bloodtransfusion and Transplantation Immunology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands [2] 2Department of Nephrology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands.

Graft-versus-host-disease (GVHD) is the most common cause of poor outcome after allogeneic stem cell transplantation (SCT). Of late, exploitation of FOXP3(+) regulatory T-cell (T (REG)) function is emerging as a promising strategy in suppression of GVHD, while preserving graft-versus-leukemia (GVL). Cyclosporine and rapamycin reduce the expansion of effector T cells by blocking interleukin (IL)-2, but signaling by IL-2 is pivotal for T(REG) homeostasis. The resolution of GVHD is critically dependent on thymus-dependent reconstitution of the immunoregulatory system. Thus, there has been concern about the impact of blocking IL-2 signaling by immunosuppressive agents on T(REG) homeostasis. Here we demonstrate in a mouse model that in contrast to rapamycin, cyclosporine compromises not only the thymic generation of CD4(+)CD25(+)FoxP3(+) T cells but also their homeostatic behavior in peripheral immune compartments. Treatment with cyclosporine resulted in a sharp reduction of peripheral CD25(+)FoxP3(+) T cells in all immune compartments studied. Prolonged rapamycin treatment allowed for thymic generation of CD4(+)FoxP3(+) T cells, whereas treatment with cyclosporine led to a reduced generation of these cells. In conclusion, cyclosporine and rapamycin differentially affect homeostasis of CD4(+)FoxP3(+) T(REG) in vivo. As peripheral tolerance induction is a prerequisite for successful treatment outcome after allogeneic SCT, these findings are of potential clinical relevance. Bone Marrow Transplantation advance online publication, 12 March 2007; doi:10.1038/sj.bmt.1705628.

PMID: 17351648 [PubMed - as supplied by publisher]

Display AbstractPlus Show 20 Sort by Send to

### Related Links

High donor FOXP3-positive regulatory T-cell (Treg) content is associated with a low risk of GVHD following HLA-matched allogeneic SCT. [Blood. 2006]

Function of the IL-2R for Thymic and Peripheral CD4+CD25+ Foxp3+ T Regulatory Cells. [J Immunol. 2007]

Lymphopenia and interleukin-2 therapy alter homeostasis of CD4+CD25+ regulatory T cells. [Nat Rev Immunol. 2005]

Oral tolerance induction with antigen conjugated to cholera toxin B subunit generates both Foxp3+CD25+ and Foxp3-CD25- CD4+ regulatory T cells. [J Immunol. 2006]

Highly efficient expansion of human CD4+CD25+ regulatory T cells for cellular immunotherapy in patients with graft-versus-host disease. [Blood. 2006]

See all Related Articles...